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(54) Preparation of a finely divided pulverous carotenoid preparation

(57) The present invention relates to a continous process for the preparation of a pulverous carotenoid, retinoid or natural colourant preparation, wherein the active ingredient is finely divided, which process comprises the steps of

a) forming a suspension of the active ingredient in a water-immiscible organic solvent optionally containing an antioxidant and/or an oil,

b) feeding the suspension of step a) to a heat exchanger and heating said suspension to 100-250°C, whereby the residence time in the heat exchanger is less than 5 see,

c) rapidly mixing the solution of step b) at a temperature in the range of 20-100°C with an aqueous solution of a swellable colloid optionally containing a stabilizer,

d) removing the organic solvent and

e) converting the dispersion of step d) into a pulverous preparation.

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Description

[0001] The present invention relates to a continous process for converting carotenoids, retinoids or natural colourants into finely divided pulverous forms which are particular required for colouring foodstuff and animal feeds.

[0002] Various processes have been described to prepare a powder containing the active ingredients with a crystallite size less than 1 micron. Most of the processes are well suited to batch processing applications.

[0003] For example, US Patent 3,998,753 describes a batch process for the preparation of a water dispersible carotenoid containing powder, wherein the carotenoid has a particle size of less than 1 micron, which process comprises (a) forming a solution of a carotenoid and an antioxidant in a volatile solvent, said solvent being selected from the group consisting of halogenated aliphatic hydrocarbons such as chloroform, carbon tetra-chloride and methylene chloride; (b) forming an aqueous solution of sodium lauryl sulfate, a water soluble carrier composition such as e.g. gelatin, a preservative and a stabilizer, and adjusting said solution to a pH of about 10 to 11 and (c) forming an emulsion of the solutions of steps (a) and (b) by mixing at a high speed and high shear; removing the organic solvent and spray drying the resulting emulsion to obtain a carotenoid powder.

[0004] In the European Patent Publication EP-0065193 B1 or the corresponding US Patent 4,522,743 a continous process for the preparation of finely divided carotenoid powders is described, in which the carotenoid has a particle size essentially below 0.5 microns. The carotenoid is dissolved in a volatile, water miscible organic solvent within less than 10 sec. at 50-200°C. The carotenoid is immediately precipitated in colloidally dispersed form from the resulting molecularly dispersed solution by rapid mixing with an aqueous solution of a swellable colloid at 0-50°C. The preparation of the carotenoid solution and the precipitation of the carotenoid are effected continuously in two mixing chambers. The resulting dispersion is freed of solvent and the dispersing medium in a conventional manner.

[0005] However, for economical and ecological reasons this process has the disadvantage that a large amount of solvent must be used.

[0006] It is an object of the present invention to provide a process that overcomes the aforesaid drawback while converting the active ingredient into finely divided pulverous form.

[0007] It has now been found that it is possible to provide a pulverous preparation wherein the active ingredient is finely divided by using a water-inmiscible organic solvent in a continous process.

[0008] Thus, the present invention relates to a continous process for the preparation of a pulverous carotenoid, retinoid or natural colourant preparation, wherein the active ingredient is finely divided, which process comprises the steps of

a) forming a suspension of the active ingredient in a water-inmiscible organic solvent optionally containing an antioxidant and/or an oil,
b) feeding the suspension of step a) to a heat exchanger and heating said suspension to 100-250°C, whereby the residence time in the heat exchanger is less than 5 sec,
c) rapidly mixing the solution of step b) at a temperature in the range of 20-100°C with an aqueous solution of a swellable colloid optionally containing a stabilizer,
d) removing the organic solvent and
e) converting the dispersion of step d) into a pulverous preparation.

[0009] The term "finely divided" denotes in the scope of the present invention a particle size of less than 1.5 micron, preferably less than 1 micron, more preferably less than 0.4 micron.

[0010] The term "active ingredient" denotes in the scope of the present invention carotenoids, retinoids or natural colourants.

[0011] Carotenoids for the purpose of the present invention in particular include beta-carotene, beta-apo-4'-carotenal, beta-apo-8'-carotenal, beta-apo-12'-carotenal, beta-apo-8'-carotenic acid, astaxanthin, canthaxanthin, zeaxanthin cryptoxanthin, citranaxanthin, lutein, lycopene, torularodin-aldehyde, torularodin-ethylester, neurosporaxanthin-ethylester, zeta-carotene or dehydroplectaniaxanthin. Also included are carotenoids of natural sources. Preferred are beta-carotene, astaxanthin, canthaxanthin, beta-apo-8'-carotenal and lycopene; more preferred is beta-carotene.

[0012] Natural colourants for the purpose of the present invention in particular include curcumine, cochineal, carmine, annatto and mixtures thereof.

[0013] Preferably the process of the invention is carried out using carotenoids.

[0014] The temperature of step b) is preferably 120-180°C, more preferably 140-170°C and the temperature of step c) is preferably 50-80°C.

[0015] The residence time in the heat exchanger is preferably 0.5-4 sec, more preferably 1-3 sec.

[0016] The term "water-inmiscible organic solvent" denotes in the scope of the present invention an organic solvent having a solubility in water of less than 10% under atmospheric pressure. Suitable water-inmiscible organic solvents for carrying out the continous process according to the invention are halogenated aliphatic hydrocarbons such as e.g. chloroform, carbon tetra-chloride and methylene chloride, water-inmiscible esters such as e.g. carbonic acid dimethylester (dimethyl carbonate), formic acid ethylester (ethyl formate) methyl -, ethyl-, or isopropylacetate; or water-inmiscible ethers such as e.g. methyl-tert. butylether and the like. Preferred are dimethyl carbonat, ethyl formate, ethyl-, or

isopropylacetate, methyl-tert. butylether.

[0017] The term "swellable colloids" denotes in the scope of the present invention gelatin, carbohydrates such as e.g. starch or starch derivatives, dextrin, pectin, gum arabic, octenylbutanedioate amylodextrin (CAPSUL™), milk protein such as e.g. casein and vegetable protein as well as mixtures thereof. Preferred are fish gelatin or starch derivatives.

[0018] To increase the stability of the carotenoid it is advantageous to add an antioxidant being selected from the group consisting of ascorbic acid, ascorbylpalmitate, dl-alpha tocopherol, mixed tocopherols, lecithine, butylhydroxytoluol, butyl-4-methoxyphenol and combinations of these compounds.

[0019] The antioxidant can be added either to the matrix solution or to the carotenoid solution or to both solutions. A preferred antioxidant for the carotenoid solution is dl-alpha tocopherol and for the aqueous phase solution it is ascorbyl palmitate.

[0020] It may be further advantageous to dissolve an oil in the carotenoid suspension, preferrably corn oil.

[0021] Reference is now made to the accompanying drawing Fig. 1 where a flow chart suitable for carrying out the process in accordance with the instant invention is diagrammatically illustrated. The whole process has to be carried out continously.

[0022] The flow chart is explained as follows:

[0023] An aqueous matrix containing a swellable colloid and optionally a stabilizer is prepared in Kettle 1.

[0024] A suspension of a carotenoid in the selected solvent is prepared in Kettle 2. The suspension may further contain an antioxidant and an oil.

[0025] The carotenoid suspension is fed by pump 6 to the heat exchanger 4. The flow rate is adjusted according to the desired residence time which is necessary to dissolve the carotenoid in the solvent at a given temperature. In the heat exchanger 4 the carotenoid suspension is heated to 100 to 250 °C, preferably to 120 to 180 °C, more preferably to 140 to 170°C and the carotene is solubilized. The heating can be done either indirectly through the heat exchanger or directly by mixing with steam at 8. The residence time in the heat exchanger is less than 5 sec, preferably 1 to 3 sec.

[0026] The matrix solution of Kettle 1 is fed by pump 7 to Kettle 3. The flow rate depends on the suspension flow rate and the required emulsion composition. In Kettle 3 the carotenoid suspension and the matrix are mixed and emulsified by using a rotor stator homogenizer to the desired particle size of the inner phase of approx. 150-400 nm. As a result of the mixing the temperature is lowered to the range 20 to 100 °C.

[0027] The dispersion obtained passes to a second heat exchanger 5 whereby the dispersion is cooled. The pressure is released to atmospheric pressure by pressure control.

[0028] The solvent is removed using conventional methods e.g. by evaporation. A pulverous composition can be isolated from the resulting dispersion by conventional methods, for example by spray drying or by using powder catch technique.

[0029] Using this invention it is possible to manufacture powders which cover very wide range of color.

[0030] The manner in which the process of the invention may readily be carried out is illustrated by the following examples. The color intensity was measured in an aqueous dispersion containing 5 ppm carotenoid and given by the calculated extinction of 1% solution in a 1 cm cuvette (E1/1-value). The average particle size has been measured by Coulter Particle Analyzer N4S. The carotenoid content was measured by UV-spectroscopy.

Example 1

[0031] Solvent: ethyl acetate, indirect heat transfer.

[0032] The aqueous matrix was prepared in Kettle 1. Thus, 1.0 kg of ascorbyl palmitate was dispersed in 27.8 kg of water at 60°C. The pH-value of this dispersion was adjusted with NaOH (20%) to 7.2-7.6. Then 3.4 kg of fish gelatin and 7.2 kg of sucrose were added. The resulting mixture was stirred until a viscous, clear solution was obtained.

[0033] 0.75 kg of all-trans-β-carotene cryst. were dispersed in Kettle 2 in a mixture of 90 g of dl-α-tocopherol, 330 g of corn oil and 7.5 kg of ethyl acetate.

[0034] The carotene suspension was fed continuously at a rate of 6 kg/h via pump 6 to the heat exchanger 4, heated to 160°C and the carotene was solubilized. The residence time in the heat exchanger was 4 sec.

[0035] The matrix solution of Kettle 1 was fed via pump 7 with a flow rate of 9.2 kg/h to Kettle 3 and mixed with the carotene solution.

[0036] The resulting emulsion was cooled in a second heat exchanger 5 to 60°C and the pressure was released to atmospheric pressure.

[0037] Ethyl acetate was removed in a thin film evaporator. The resulting emulsion showed a particle size of the inner phase of 225 nm and was spray dried. A powder with the following specifications was obtained: 11.6 % carotene content, $E\ ^1/_1 = 1015$, λ max. 440-460 nm. The powder was well soluble in cold water with an intense red coloration.

Example 2

Solvent: isopropyl acetate, direct heat transfer (steam)

[0038] 1.25 kg of Ascorbyl palmitate was dispersed in 30.9 kg water at 60°C according to Example 1. The pH-value of this dispersion was adjusted with NaOH (20%) to 7.2-7.6. Then 5.1 kg of fish gelatin and 7.1 kg of sucrose were added. The resulting mixture was stirred until a viscous, clear solution was obtained.

[0039] 0.75 kg of Canthaxanthin cryst. were dispersed in Kettle 2 in a mixture of 0.10 kg of dl-α-tocopherol, 0.36 kg of corn oil and 6.25 kg of isopropyl acetate.

[0040] The canthaxanthin suspension was fed continuously at a rate of 6 kg/h via pump 6 to the mixing chamber where the temperature was raised by injection of steam to 170°C. Then, the hot canthaxanthin dispersion passed within 2 sec. through the heat exchanger 4 where the canthaxanthin was solubilized.

[0041] The matrix solution of Kettle 1 was fed via pump 7 with a flow rate of 8.1 kg/h to Kettle 3 and mixed with the canthaxanthin solution.

[0042] The resulting emulsion is cooled in heat exchanger 5 to 60°C and the pressure was released to atmospheric pressure.

[0043] Isopropyl acetate was removed in a thin film evaporator. The resulting emulsion showed a particle size of the inner phase of 213 nm and was spray dried. A powder with the following specifications was obtained: 12.3 % canthaxanthin content, E $^1/_1$ =905, λ max. 470-485 nm. The powder was well soluble in cold water with an intense cherry-red coloration.

Example 3

Solvent: isopropyl acetate, direct heat transfer (steam)

[0044] 10.3 kg of Fish gelatin, 20.6 kg of sugar and 2.78 kg of ascorbyl palmitate were dissolved in 27.56 kg of water in Kettle 1. The pH-value of this matrix was adjusted with NaOH (20%) to 7.2 - 7.6.

[0045] 6.68 kg of β-Carotene, 0.84 kg of dl-α-tocopherol and 3.34 kg of corn oil were dispersed in 33.4 kg of isopropyl acetate in Kettle 2.

[0046] The β-carotene suspension was fed by pump 6 with a flow rate of 25 kg/h to the heat exchanger 4 where it was mixed with steam to reach an outlet temperature of 160°C. The residence time in the heat exchanger 4 was 1.0 sec. The matrix was pumped by pump 7 with a flow rate of 34.5 kg/h to Kettle 3 where the solved β-carotene was mixed with the matrix and emulsified in it. The emulsion was cooled down to 60°C in heat exchanger 5.

[0047] Isopropyl acetate was removed from the emulsion by using a vertical evaporator. The resulting emulsion showed a particle size of the inner phase of 220 nm and was spray dried.

[0048] The final product had a β-carotene content of 11.3%; E1/1: 1159, λ max. 440-460 nm. The powder was well soluble in water. The solution had a very intensive yellow color.

Example 4

Solvent: isopropyl acetate, direct heat transfer (steam).

[0049] 9.25 kg of Fish gelatin, 18.5 kg of sugar and 2.5 kg of ascorbyl palmitate were dissolved in 30.25 kg of water in Kettle 1. The pH-value of this matrix was adjusted with NaOH (20%) to 7.2 -7.6.

[0050] 6.0 kg of β-Carotene, 0.75 kg of dl-α-tocopherol and 3.0 kg of corn oil were dispersed in 30.0 kg of isopropyl acetate in Kettle 2.

[0051] The β-carotene suspension was fed by pump 6 with a flow rate of 20 kg/h to the heat exchanger 4 where it was mixed with steam to reach an outlet temperature of 158°C. The residence time in the heat exchanger 4 was 1.3 sec. The matrix was pumped by pump 7 with a flow rate of 30.4 kg/h to Kettle 3 where the solved β-carotene was mixed with the matrix and emulsified in it. The emulsion is cooled down to 60°C in heat exchanger 5.

[0052] Isopropyl acetate was removed from the emulsion by using a vertical evaporator. The resulting emulsion showed a particle size of the inner phase of 240 nm and was spray dried.

[0053] The final product has a β-carotene content of 11.2%, E1/1:795, λ max. 440-460 nm. The powder was well soluble in water, the solution has a very intensive red color.

Example 5

Solvent: methylene chloride, direct heat transfer (steam).

[0054] 9.25 kg Fish Gelatin, 18.5 kg of sugar and 2.5 kg of Ascorbyl palmitate were dissolved in 30.25 kg of water in Kettle 1. The pH-value of this matrix was adjusted with NaOH (20%) to 7.2 - 7.6.

[0055] 6.0 kg of β-Carotene, 0.75 of kg dl-α-tocopherol and 3.0 kg of corn oil were dispersed in 30.0 kg of methylene chloride in Kettle 2.

[0056] The β-carotene suspension was fed by pump 6 with a flow rate of 20 kg/h to the heat exchanger 4 where it was mixed with steam to reach an outlet temperature of 145°C. The residence time in the heat exchanger 4 was 1.3 sec. The matrix was pumped by pump 7 with a flow rate of 30.4 kg/h to the Kettle 3 where the solved β-carotene was mixed with the matrix and emulsified in it. The emulsion was cooled down to 35°C in heat exchanger 5.

[0057] Methylene chloride was removed from the emulsion by using a vertical evaporator. The resulting emulsion showed a particle size of the inner phase of 196 nm and was spray dried.

[0058] The final product has a β-carotene content of 9.9%, E1/1: 1120, λ_{max}: 440-460 nm. The powder was well soluble in water, the solution has a very intensive yellow color.

Claims

1. A continous process for the preparation of a pulverous carotenoid, retinoid or natural colourant preparation, wherein the active ingredient is finely divided, which process comprises the steps of

a) forming a suspension of the active ingredient in a water-inmiscible organic solvent optionally containing an antioxidant and/or an oil,
b) feeding the suspension of step a) to a heat exchanger and heating said suspension to 100-250°C, whereby the residence time in the heat exchanger is less than 5 sec,
c) rapidly mixing the solution of step b) at a temperature in the range of 20-100°C with an aqueous solution of a swellable colloid optionally containing a stabilizer,
d) removing the organic solvent and
e) converting the dispersion of step d) into a pulverous preparation.

2. A process according to claim 1, wherein the active ingredient has a particle size of less than 1.0 micron, preferably less than 0.4 micron.

3. A process according to claim 1 or 2, wherein the temperature of step b) is 120-180°C, preferably 140-170°C and the temperature of step c) is 50-80°C.

4. A process according to any one of claims 1-3, wherein the residence time in the heat exchanger is 0.5-4 sec, preferably 1-3 sec..

5. A process according to any one of claims 1-4, wherein the water-inmiscible organic solvent is dimethyl carbonate, ethyl formate, ethyl-, or isopropylacetate, methyl-tert. butylether or methylene chloride.

6. A process according to any one of claims 1-5, wherein the active ingredient is a carotenoid.

7. A process according to claim 6, wherein the carotenoid is selected from the group consisting of beta-carotene, beta-apo-4'-carotenal, beta-apo-8'-carotenal, beta-apo-12'-carotenal, beta-apo-8'-carotenic acid, astaxanthin, canthaxanthin, zeaxanthin cryptoxanthin, citranaxanthin, lutein, lycopene, torularodin-aldehyde, torularodin-ethylester, neurosporaxanthin-ethylester, zeta-carotene or dehydroplectaniaxanthin.

8. A process according to any one of claims 1-7, wherein the swellable colloid is selected from the group consisting of gelatin; starch or starch derivatives, dextrin, pectin, gum arabic, octenylbutanedioate amylodextrin, milk protein, vegetable protein as well as mixtures thereof.

9. A process according to any one of claims 1-8, wherein the antioxidant is selected from the group consisting of ascorbic acid, ascorbylpalmitate, dl-alpha tocopherol, mixed tocopherols, lecithine, butylhydroxytoluol, butyl-4-methoxy-phenol and combinations of these compounds.

10. A process according to any one of claims 1-9, wherein the solution of the active ingredient is effected either indirectly through the heat exchanger or directly by mixing with steam and the precipitation of the active ingredient in the swellable colloid is effected continuously in a mixing device connected in series.

11. A pulverous preparation prepared by a process as claimed according to any one of claims 1-10 and containing from 0.5-25% by weight of an active ingredient.

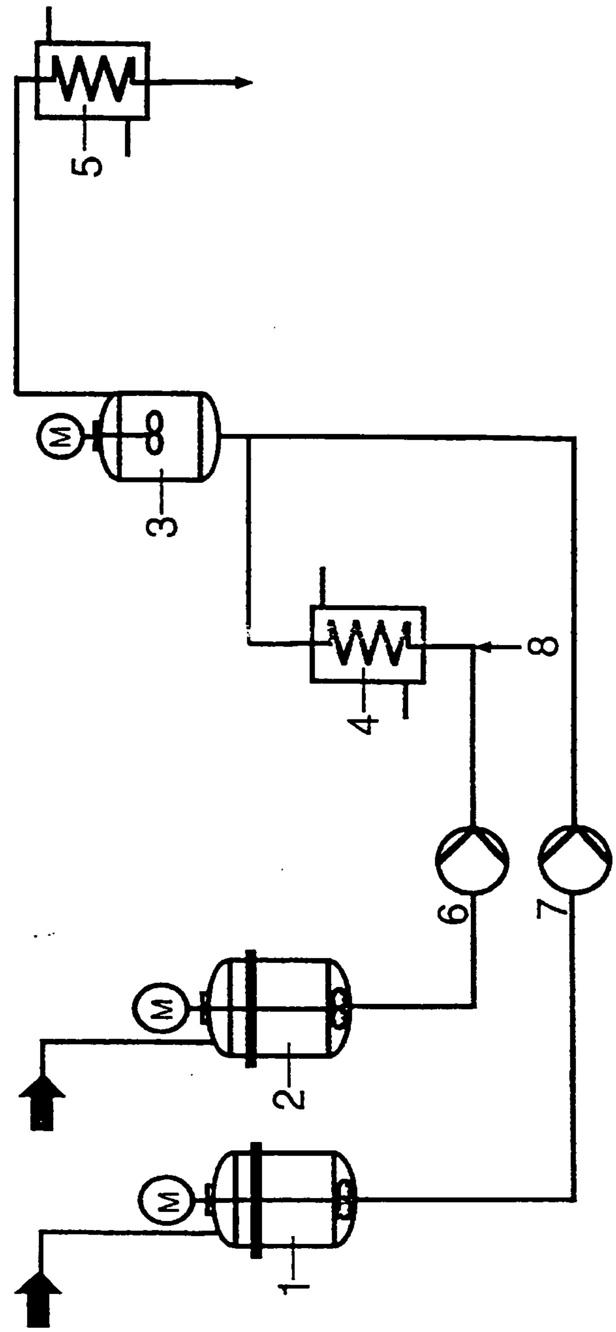

Fig. I

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EUROPEAN SEARCH REPORT

Application Number
EP 99 10 3239

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	US 3 790 688 A (WALTER W ET AL) 5 February 1974 * claim 1 *	1-11	A23L1/275
X	US 4 844 934 A (LUEDDECKE ERIK ET AL) 4 July 1989 * examples 1,2 *	1-11	
X	US 5 364 563 A (CATHREIN ERNST ET AL) 15 November 1994 * column 3, line 33 - line 36; examples 1,2 *	1-11	
X,D	US 4 726 955 A (HORN DIETER ET AL) 23 February 1988	1-11	
Y	* examples 1-8 *	1-11	
X	US 4 522 743 A (HORN DIETER ET AL) 11 June 1985 * examples 1-17 *	1-11	**TECHNICAL FIELDS SEARCHED (Int.Cl.6)**
X,D	US 3 998 753 A (ANTOSHKIW THOMAS WILLIAM ET AL) 21 December 1976 * examples 1-4 *	1-11	A23L
X	DE 12 11 911 B (HOFFMANN-LA ROCHE & CO AG) 3 March 1966	1-11	
Y	* column 3, line 41 - line 53; examples 1-6 *	1-11	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	6 May 1999	Bendl, E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 10 3239

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06-05-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3790688 A	05-02-1974	NONE	
US 4844934 A	04-07-1989	DE 3610191 A	01-10-1987
		AU 593081 B	01-02-1990
		AU 7062887 A	01-10-1987
		DE 3779466 A	09-07-1992
		EP 0239086 A	30-09-1987
		JP 7096649 B	18-10-1995
		JP 62240364 A	21-10-1987
US 5364563 A	15-11-1994	AT 96312 T	15-11-1993
		DE 59003205 D	02-12-1993
		DK 410236 T	13-12-1993
		EP 0410236 A	30-01-1991
		JP 2572877 B	16-01-1997
		JP 3066615 A	22-03-1991
US 4726955 A	23-02-1988	DE 3611229 A	08-10-1987
		DE 3784534 A	15-04-1993
		DK 170287 A	05-10-1987
		EP 0239949 A	07-10-1987
US 4522743 A	11-06-1985	DE 3119383 A	02-12-1982
		AT 16814 T	15-12-1985
		AU 553623 B	24-07-1986
		AU 8372582 A	18-11-1982
		CA 1202809 A	08-04-1986
		DK 216082 A,B,	16-11-1982
		DK 334188 A,B,	17-06-1988
		EP 0065193 A	24-11-1982
		JP 1670100 C	12-06-1992
		JP 3035347 B	27-05-1991
		JP 57195161 A	30-11-1982
US 3998753 A	21-12-1976	AT 351912 B	27-08-1979
		AT 625675 A	15-01-1979
		BE 832331 A	12-02-1976
		DE 2534091 A	26-02-1976
		FR 2281961 A	12-03-1976
		GB 1502895 A	08-03-1978
		JP 51041732 A	08-04-1976
		NL 7509586 A	17-02-1976
DE 1211911 B		NONE	

EPO FORM P0459

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